Detection of low-volume blood loss: Compensatory reserve versus traditional vital signs

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BACKGROUND: Humans are able to compensate for low-volume blood loss with minimal change in traditional vital signs. We hypothesized that a novel algorithm, which analyzes photoplethysmogram (PPG) wave forms to continuously estimate compensatory reserve would provide greater sensitivity and specificity to detect low-volume blood loss compared with traditional vital signs. The compensatory reserve index (CRI) is a measure of the reserve remaining to compensate for reduced central blood volume, where a CRI of 1 represents supine normovolemia and 0 represents the circulating blood volume at which hemodynamic decompensation occurs; values between 1 and 0 indicate the proportion of reserve remaining.

METHODS: Subjects underwent voluntary donation of 1 U (approximately 450 mL) of blood. Demographic and continuous noninvasive vital sign wave form data were collected, including PPG, heart rate, systolic blood pressure, cardiac output, and stroke volume. PPG wave forms were later processed by the algorithm to estimate CRI values.

RESULTS: Data were collected from 244 healthy subjects (79 males and 165 females), with a mean (SD) age of 40.1 (14.2) years and mean (SD) body mass index of 25.6 (4.7). After blood donation, CRI significantly decreased in 92% (0.05; 95% confidence interval [CI], 88 95%) of the subjects. With the use of a threshold decrease in CRI of 0.05 or greater for the detection of 1 U of blood loss, the receiver operating characteristic area under the curve was 0.90, with a sensitivity of 0.84 and specificity of 0.86. In comparison, systolic blood pressure (52%; 95% CI, 45 59%), heart rate (65%; 95% CI, 58 72%), cardiac output (47%; 95% CI, 40 54%), and stroke volume (74%; 95% CI, 67 80%) changed in fewer subjects, had significantly lower receiver operating characteristic area under the curve values, and significantly lower specificities for detecting the same volume of blood loss.

CONCLUSION: Consistent with our hypothesis, CRI detected low-volume blood loss with significantly greater specificity than other traditional physiologic measures. These findings warrant further evaluation of the CRI algorithm in actual trauma settings. (*J Trauma Acute Care Surg*. 2014;77: 892 898. Copyright © 2014 by Lippincott Williams & Wilkins)

LEVEL OF EVIDENCE: Diagnostic study, level II.

KEY WORDS: Machine learning; compensatory reserve index; photoplethysmogram; acute blood loss.

One of the most difficult tasks in clinical medicine is the assessment of decreasing volume status.[1] This evaluation is usually made by physical examination and a review of the patient's traditional vital signs as follows: heart rate (HR), blood pressure (BP), respiratory rate, and oxygen saturation. These vital signs are, however, notoriously unreliable.[2,3] As computing power and computational methods improve, it is now evident that current monitoring technology is allowing physiologic information to pass by unseen and unharnessed. Many pathologic states have been characterized by analysis of simple, continuous physiologic wave forms,[1,4–7] and previous studies have demonstrated that photoplethysmogram (PPG) wave forms obtained with a pulse oximeter sensor significantly change with volume loss.[5] With this information in mind, our group hypothesized that advanced feature extraction techniques and machine-learning technologies originally developed for navigation of unmanned military vehicles could be applied to the PPG and other noninvasive pulsatile wave forms to continuously assess central volume status. To test this concept, pulsatile wave forms were recorded from healthy volunteers during lower-body negative-pressure (LBNP) experiments conducted at the US Army Institute of Surgical Research. LBNP experiments redistribute blood volume from the upper body to the pelvis and lower extremities to simulate hemorrhage from normovolemia to decompensation (systolic BP [SBP] < 80 mm Hg). Several studies have confirmed that many of the physiologic derangements that are known to occur during severe hemorrhage also occur during the application of LBNP.[4,5,8–13]

In our initial experiments, PPG wave forms were collected from human LBNP subjects who underwent controlled reductions of central blood volume from normovolemia to decompensation. Advanced feature extraction and machine-learning

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methods were used to extract information from the PPG wave form. The resulting algorithm, used to calculate the compensatory reserve index (CRI), continuously analyzes the entirety of each pulsatile wave form to trend subtle features that correspond with varying degrees of central volume loss.[6,14,15] The algorithm is designed to estimate the following quantity:

$$CRI = 1 - [BLV/BLV_{HDD}]$$

where BLV is the current blood loss volume of the patient and BLV_{HDD} is the blood loss volume at which the patient will experience hemodynamic decompensation.[12] CRI ranges from 1 to 0 and corresponds to the body's ability to compensate for acute intravascular volume loss (Fig. 1). A CRI of 1 equates to supine normovolemia, while a CRI of 0 equates to being volume depleted and unable to compensate (cardiovascular collapse). CRI values between 1 and 0 indicate the proportion of reserve remaining before hemodynamic decompensation—much like the fuel gauge of a car indicates the amount of fuel remaining in the tank. When a patient loses intravascular volume because of bleeding or dehydration, the "tank" empties and CRI goes down. With appropriate fluid resuscitation, the tank refills and CRI goes up. Based on our human LBNP experiments, we hypothesized that changes in CRI could be used to detect low-volume blood loss with greater sensitivity and specificity than traditional vital signs. We tested this by studying voluntary blood donors.

PATIENTS AND METHODS

This study was conducted under a protocol reviewed and approved by The Colorado Multi-Institutional Review Board and the US Army Human Research Protection Office. Informed consent was obtained from all subjects participating in this protocol.

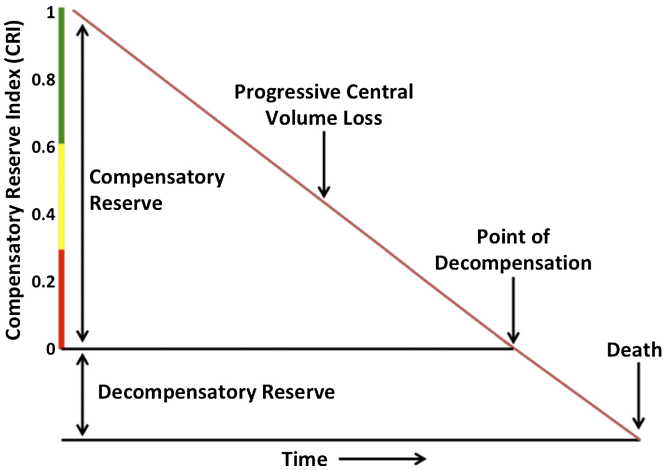

Figure 1. Schematic of the CRI. The CRI is indicative of the individual-specific proportion of intravascular volume remaining before the onset of cardiovascular collapse. The *red line* shows a hypothetical decline in CRI over time in the setting of volume loss. A CRI of 1 represents supine normovolemia, whereas a CRI of 0 represents the point at which hemodynamic decompensation develops.

Consecutive patients age 18 years to 89 years were approached for study enrollment immediately before planned voluntary donation of 1 U of blood at the Children's Hospital Colorado blood donation center. Subjects were given the option of having at least 4 minutes of wave form data collected before blood donation to construct a no blood loss data set. All enrolled subjects had continuous noninvasive wave form data recorded for the duration of their blood donation, including PPG wave forms (OEM III pulse oximeter, Nonin, Minneapolis, MN), and a noninvasive BP wave form (ccNexfin, Edwards Lifesciences, Irvine, CA) from one of three middle fingers of the hand opposite the venipuncture site for blood donation. A flow meter (Transonic Systems, Ithaca, NY) was used to continuously monitor the blood flow rate as blood flowed from the subject into a donor collection bag. Demographic and clinical information were also collected. No changes were made to the standard blood donation protocol.

Subjects were included in the final analysis if they had a successful blood draw (>400 mL blood donated), if wave form recordings were complete and if wave form recordings could be aligned with the flow meter. After data collection, the PPG wave form was used to calculate CRI. Continuous HR, SBP, cardiac output (CO), and stroke volume (SV) values were provided by the ccNexfin. Averages are presented as the mean (standard deviation, SD), and p values are reported as <0.001 when lower. Parameter values at the beginning of blood donation were compared with values obtained at the end of blood donation, using the first and last 65 samples (1 sample = 1 heart beat). A significant decrease in each parameter was determined using a two-sided t test with power of 0.9 and α of 0.05, with 95% confidence intervals (CIs) reported. A binary classifier was constructed to determine the optimal threshold for the change in parameter value associated with 1 U of blood loss. This was done by comparing data from the beginning and end of premonitoring (only in subjects with >4 minutes of monitoring before donation) to the data from the beginning and end of the blood donation, using change in the parameter over the interval as the sole measure for the classification of blood loss. The effectiveness of each of the binary classifiers (one per parameter) was assessed using receiver operating characteristic area under the curve (ROC AUC) analysis and estimation of sensitivity and specificity. All statistical analysis was conducted with Matlab Statistical Toolbox (The MathWorks, Inc., Natick, MA).

RESULTS

Demographics

There were 317 subjects enrolled in this study. Of these subjects, 9 had unsuccessful blood draws and 64 had insufficient data for further analysis. Data from the remaining 244 subjects were used in the final analysis. PPG wave form data were analyzed for 244 healthy volunteer subjects (79 males and 165 females), with a mean (SD) age of 40.1 (14.2) years (range, 18–78 years) and a mean (SD) body mass index (BMI) of 25.6 (4.7) (range, 17.2–46.4). Noninvasive BP wave form data were analyzed for 204 of 244 subjects (66 males and 138 females), with a mean (SD) age of 40.5 (14.3) years (range, 18–78 years) and a mean (SD) BMI of 25.5 (4.7) (range, 17.2–46.4). To have

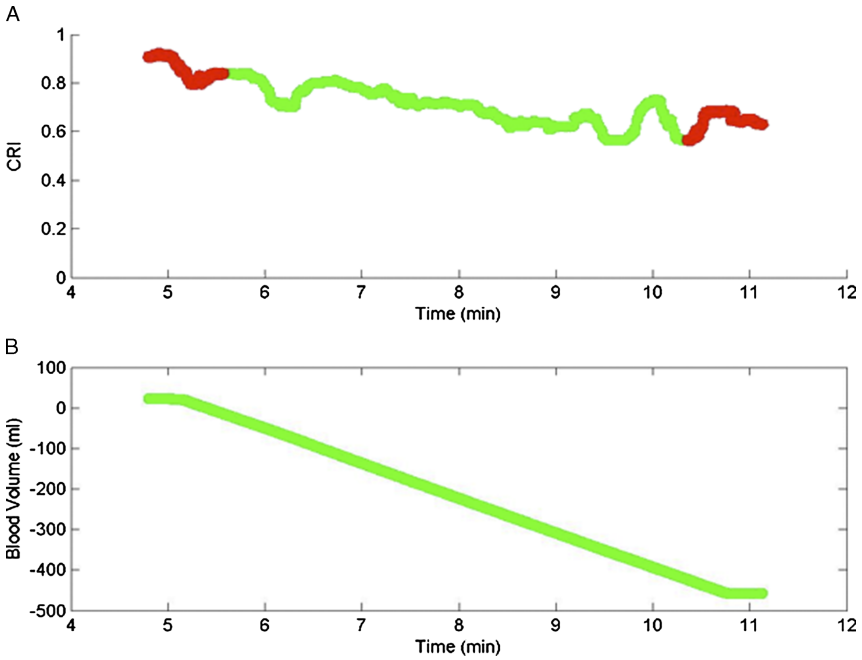

Figure 2. Example of data used for comparison of parameters. These graphs represent data collected from one subject during blood donation. *A,* CRI values estimated during the donation of a unit of blood. The portion of the line highlighted in red signifies the values that were used to compare the beginning and end of blood donation. *B,* Blood volume removed as determined by the flow meter.

data representing no blood loss, 122 of 244 subjects (29 males and 83 females, 93 with noninvasive BP wave form data) agreed to more than 4 minutes of wave form data collection before blood donation, with a mean (SD) age of 37.5 (13.3) years (range, 19–68 years) and a mean (SD) BMI of 25.6 (5.2) (range, 17.6–46.4). There were no statistical differences in the means of any of these subgroups ($p > 0.05$). The mean (SD) blood volume removed was 459 (9) mL (range, 418–491 mL), and the mean (SD) duration of blood donation was 9 (2) minutes (range, 2–20 minutes).

Parameter Change Due to Blood Donation

We compared data collected during the first and last 65 heart beats of blood donation to determine whether parameter changes between the two intervals were significant. An example of the values compared is shown in Figure 2. The mean initial and final values for each parameter are shown in Table 1. CRI, HR, and SV significantly changed after blood donation. There were no statistical differences in SBP or CO after blood donation. CRI significantly decreased in 92% of the subjects (95% CI, 88–95%). By comparison, fewer subjects had significant changes in all other measured parameters (Table 2). SBP significantly decreased in 52% of the subjects (95% CI, 45–59%), HR in 65% of the subjects (95% CI, 58–72%), CO in 47% of the subjects (95% CI, 40–54%), and SV in 74% of the subjects (95% CI, 67–80%).

ROC AUC, Sensitivity, and Specificity

The optimal threshold change for detecting 1 U of blood loss was assessed for each parameter measured. The ROC curve was then constructed, and ROC AUC, sensitivity, and specificity were calculated. For CRI, the optimal threshold for detecting 1 U of blood loss was a decrease of 0.05 or more, the ROC AUC was 0.9, and the sensitivity and specificity were 0.84 and 0.86, respectively (Fig. 3). SBP, with a threshold

TABLE 1. Comparison of Initial and Final Parameter Values From Blood Donation

Parameter	Initial Mean (SD)	Final Mean (SD)	Two-Sample *t* Test
CRI	0.78 (0.11)	0.63 (0.15)	$p \leq 0.001$*
SBP, mm Hg	141 (22)	138 (20)	p 0.09
HR, beats/min	72 (11)	75 (11)	$p < 0.001$*
CO, L/min	6.1 (1.5)	5.9 (1.4)	p 0.15
SV, mL	85 (18)	78 (17)	$p \leq 0.001$*

*Statistically significant values.

The initial and final mean (SD) parameter values obtained during blood donation are reported. A two-sample *t* test was used to determine if the mean changed before and after blood loss.

TABLE 2. Percentage of Subjects With a Significant Change After Blood Donation

Parameter	% With Significant Change	95% CI
CRI	92%	88 95%
SBP	52%	45 59%
HR	65%	58 72%
CO	47%	40 54%
SV	74%	67 80%

The percentage of patients who experienced a significant change in the parameters measured during blood donation is reported.

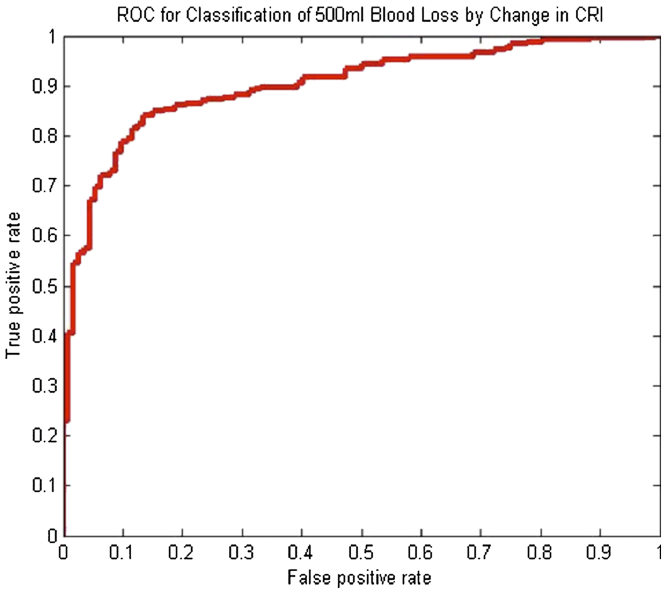

Figure 3. The ROC curve for the CRI. The ROC curve represents the efficacy of the CRI for detecting the loss of 1 U of blood using a threshold decrease in CRI of 0.05 or more. The AUC is 0.90, with a sensitivity of 0.84 and specificity of 0.86.

decrease of 8 mm Hg or more, had an ROC AUC of 0.84, with a sensitivity and specificity of 0.90 and 0.58, respectively. HR, with a threshold increase of 7 beats/min or more, had an ROC AUC of 0.55, with a sensitivity and specificity of 0.98 and 0.04, respectively. CO, with a threshold decrease of 0.5 L/min or more, had an ROC AUC of 0.72, with a sensitivity and specificity of 0.92 and 0.39, respectively. SV, with a threshold decrease of 2.7 mL or more, had an ROC AUC of 0.78, with a sensitivity and specificity of 0.92 and 0.42, respectively. When compared with all other parameters, CRI had the highest ROC AUC and highest specificity, with comparable sensitivity for the detection of 1 U of blood loss (Table 3).

DISCUSSION

Exsanguination is the second most common cause of trauma-related death and is the leading cause of death within 48 hours of hospital admission.[16] Humans have a multitude of survival compensatory neuroendocrine mechanisms, which allow them to tolerate up to 30% of circulating blood volume loss before changes in traditional vital signs are clearly evident.[7,17] Because some individuals are more tolerant than others to acute blood loss, it is difficult to predict how an individual will respond to fluid resuscitation.[18] Furthermore, a patient may appear to be adequately volume resuscitated based on normalization of vital signs but in fact be underresuscitated and have an oxygen debt, which can lead to organ dysfunction and contribute to trauma-related death.[19,20] Relying on traditional vital signs to identify hypovolemic hemodynamic instability can be problematic because traditional vital signs may not change until late during the compensatory phase of volume loss. They are also not specific to volume loss and can be abnormal for a number of reasons.[19] Thus, early detection of bleeding would facilitate appropriate and possibly lifesaving volume resuscitation. Here, we show that a new algorithm that is used to calculate the compensatory reserve index can quickly, reliably, and noninvasively detect relatively small volumes of blood loss in healthy adults. A decrease of 0.05 in CRI has a sensitivity and specificity of 0.84 and 0.86 for detecting the loss of 1 U of blood. Other vital sign parameters, including HR, SBP, CO, and SV, were unable to reliably detect the same small volume of blood loss. While these parameters had relatively high sensitivity, their poor specificity prevented them from discriminating when blood loss was occurring. Our findings suggest that CRI could be used to monitor and detect low-volume blood loss before it was otherwise apparent.

Various methods in addition to monitoring traditional vital signs are used to assess volume status in traumatically injured and potentially bleeding individuals. Like traditional vital signs, these methods are known to have significant limitations. Physical examination findings of hypovolemia include large postural pulse changes or postural dizziness, but these cannot be assessed in the majority of trauma patients and are often absent after only moderate amounts of blood loss. Other physical examination findings such as skin turgor and capillary refill are not indicative of volume loss in adults.[21] Laboratory values such as hemoglobin and hematocrit are often used to assess circulating blood volume, but the timeliness and accuracy of these laboratory values are limited, especially in patients who have received significant crystalloid resuscitation.[22] Techniques have been described to discriminate between true anemia and hemodilution; however, they require additional tests using specific equipment.[22] Base deficit (BD) is a rapidly and widely available serum laboratory marker of systemic acidosis that increases with hypoxemia and/or shock. In trauma settings, the degree of BD correlates with blood transfusion requirement, risk of multiorgan failure, and mortality.[23,24] BD can increase, however, because of any derangement causing metabolic acidosis and is not limited to intravascular volume loss. Similarly, serum lactate has been used as a marker of acute blood loss but is also nonspecific.[25,26]

Many newer sophisticated parameters have been studied in the evaluation of volume status and fluid responsiveness.[1,18,27–29] Static parameters have not performed well, and while dynamic parameters are better at predicting fluid response, their clinical use has not been widely accepted because of difficultly in application and/or interpretation. Parameters such as SV variation and pulse pressure variation are limited to the evaluation of mechanically ventilated patients, are of limited

TABLE 3. Threshold, ROC AUC, Sensitivity, and Specificity for Detecting 1 U of Blood Loss

Parameter	Threshold (Δ)	ROC AUC	Sensitivity	Specificity
CRI	0.05	0.90	0.84	0.86
SBP, mm Hg	8	0.84	0.90	0.58
HR, beats/min	7	0.55	0.98	0.04
CO, L/min	0.5	0.72	0.92	0.39
SV, mL	2.7	0.78	0.92	0.42

The optimal threshold value (reported as the change from initial value, Δ) of each parameter measured during blood donation to detect the loss of 1 U of blood was calculated, along with the ROC AUC, sensitivity, and specificity of each parameter.

value in children,[30] and require an invasive monitoring device. Near-infrared spectroscopy (NIRS) is a noninvasive technology that uses the near-infrared light spectrum to penetrate several centimeters into human tissue.[31] Spectral changes due to the oxygenation level in hemoglobin and myoglobin permit NIRS to measure tissue perfusion, which is altered peripherally during the compensatory phase of hemorrhage.[31] NIRS has been studied using LBNP and demonstrates decreased muscle oxygenation in advance of changes in traditional vital signs due to central hypovolemia.[32] NIRS was also able to discriminate between normal controls and patients at various levels of shock but was inferior to BP in this study.[33] NIRS performs similarly to BD and BP in predicting the development of multiorgan dysfunction and death from traumatic shock.[34] Perhaps, most important is that NIRS has not been shown to predict the time to cardiovascular instability or distinguish individuals who have relatively low tolerance to reduced circulating central blood volume and are subsequently at highest risk for decompensating and developing shock.

Our interest in the PPG wave form for the assessment of intravascular volume status is not unique. Its ability to demonstrate the interaction between cardiac pulsation, arterial/venous pressure, and peripheral vascular tone has led many researchers to study the PPG wave form in an attempt to characterize subtle changes in the circulation.[7] Most studies focus on the beat-to-beat variation of the PPG wave forms. Various types of analysis of PPG wave form variability can detect small-volume blood loss in spontaneously breathing patients without appreciable changes in HR or BP.[35,36] An algorithm called the pleth variability index has been used to detect hemodynamic changes induced by passive leg raising[37] and predicts fluid responsiveness in mechanically ventilated adult patients.[38,39] It has also been reported, however, that PPG variation shows a considerable degree of intersubject variability, making it difficult to distinguish between hypovolemic and nonhypovolemic subjects based on a single measurement.[7] Thus, like many other parameters used to detect hypovolemia, it must be compared with itself over time to give meaningful information.

There are several unique aspects of the CRI that make it ideal for clinical application in comparison with other parameters. It is easily and noninvasively determined from a PPG wave form obtained with a pulse oximeter sensor. CRI is calculated after 30 heart beats and is recalculated beat-to-beat in a continuous fashion. Our previous experiments demonstrate that it is easy to use and understand,[40] with lower numbers representing diminishing cardiovascular reserve and higher numbers indicating volume repletion. CRI has also been shown to differentiate individuals who have high tolerance to central volume loss from those with low tolerance.[12] Lastly, CRI requires no reference measurement to normovolemia, with a scale that represents the same information for individual subjects.[14,15] Unlike other parameters, which produce raw uninterpreted information that require synthesis by the clinician, CRI interprets the wave form data for the clinician. The data presented here suggest that CRI can detect hemodynamic changes secondary to low-volume blood loss, which are not detectable by other traditional vital sign parameters. While a single CRI value cannot predict how rapidly a bleeding patient will decompensate, these data show that changes in CRI over a short period are more specific for blood loss than traditional vital signs. This greater specificity for acute small-volume loss could potentially alert a clinician at an earlier point in time that resuscitative maneuvers are indicated.

There are several limitations to this study. The first is related to the blood donor study population enrolled. Most subjects were relatively healthy middle-aged females, with normal to overweight BMI. While this does not represent the wide range of patients who are subject to traumatic blood loss, the average age is similar to that reported in epidemiologic studies of trauma.[16] The second limitation is related to the clinical scenario for blood loss: the sympathetic discharges related to traumatic injury were absent, as were the alterations in hemodynamics related to the treatment of trauma patients. To further assess the compensatory reserve and account for these limitations, we have begun prospectively enrolling traumatically injured adults into a study in which a small custom-made device is used to record the PPG wave form from a pulse oximeter sensor. This device follows the patient throughout resuscitation. The PPG wave forms will be used to generate CRI values, which will be compared with each patient's clinical findings. If we find that machine learning and feature extraction of PPG wave forms anticipate significant bleeding and hemodynamic decompensation in advance of changes in traditional vital signs, we anticipate that the clinical measurement of the compensatory reserve will dramatically change how volume status is assessed and repleted in traumatically injured patients.

AUTHORSHIP

C.L.S. and S.L.M. conducted the literature search. J.M., G.Z.G., V.A.C., and S.L.M. contributed to the study's design. C.L.S. collected the data. J.M., G.Z.G. contributed to data analysis. C.L.S. and S.L.M. performed data interpretation. C.L.S., J.M., G.Z.G., and S.L.M. wrote the manu script, which J.M., G.Z.G., V.A.C., and S.L.M. critically revised.

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DISCLOSURE

The following authors have a conflict of interest: Jane Mulligan (own ership), Greg Z. Grudic (ownership), and Steven L. Moulton (owner ship). This work is supported by the US Army Medical Research and Material Command (USAMRMC) under grants W81XWH 11 2 0085 and W81XWH 12 2 0112.

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EDITORIAL CRITIQUE

Mild degrees of hemorrhagic shock, sometimes termed "compensated shock," are common in trauma patients. Typical vital signs, such as blood pressure, heart rate, and respiratory rate, are neither sensitive nor specific for identifying this condition. Clinicians are readily fooled into a sense of complacency, possibly missing clinically important injuries. Consequently, there is need for a readily-available, non-invasive, continuously-monitored physiologic parameter that would not only identify early shock, but would also serve to monitor the adequacy of resuscitation.

For this purpose, Stewart et al. have been studying the use of the compensatory reserve index (CRI), derived from photoplethysmogram wave forms. Previous work has demonstrated the utility of this technique to monitor simulated blood loss using lower-body negative pressure. Patient waveforms are compared to previously established waveform analysis during states of supine normovolemia (CRI=1) to cardiovascular decompensation (CRI=0) to generate the CRI for that patient at that time point.

In the current study, Stewart et al. demonstrated that the change in CRI between the beginning and end of elective blood donation was able to detect low-volume blood loss in healthy volunteers better than standard vital signs and even noninvasively determined cardiac output and stroke volume. A recent study of military volunteers from the Israeli Defense Forces had similar results.

Though the use of CRI seems promising, the current study has important limitations to consider. First, clinically, patients have mild hemorrhage prior to presentation, so there is no baseline for comparison. More work needs to be done to determine if a single value of CRI can detect mild hemorrhage with an appropriate cutoff value.

Second, several physiologic parameters, such as lactate or base deficit levels, pulse pressure variability in mechanically ventilated patients, heart rate variability, and tissue oxygenation by near infrared spectroscopy, have already been studied as possible markers of mild hypovolemia or of the adequacy of resuscitation. CRI needs to be compared to these other parameters. Though the authors point out that photoplethysmography can be very portable, there is increasing data on the utility of prehospital, point-of-care lactate measurements that can identify trauma patients at increased risk of death despite relatively normal vital signs.

Stewart et al. should be commended for developing a novel technology that may become clinically useful for both detecting mild hemorrhage and for optimizing resuscitation from hemorrhagic shock. More work needs to be done in actual trauma patients. Future studies also ought to compare the CRI with lactate, base deficit, or other parameters. In addition, the change in CRI during resuscitation could prove to be very useful for monitoring the adequacy of resuscitation. Ultimately, this work may alter our approach to monitoring trauma patients in a clinically significant way.

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